Final Technical Report

NCC 2-556

Granting Agency: National Aeronautics and Space Administration

NASA Grant Number: NCC 2-556

Title: Renal Function Alterations During Skeletal Muscle Disuse in Simulated Microgravity.

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Period of Project under current P.I.: 1/1/92-10/31/92

Other Personnel: Stacey Provost, Staff Research Associate
Margarida Mendonca, Staff Research Associate

Background: This grant was originally awarded to Dr. David J. Sartoris, Associate Professor in Residence, Department of Radiology, School of Medicine, University of California, San Diego. The original intent of this project was to utilize the MRI facility at University of California, San Diego Medical Center when it was apparent that the MRI facility would be available for research use. Unfortunately, the high demand for the MRI facility for clinical diagnosis precluded any diversion of time to research purposes. It was also deemed unlikely that the MRI facility would be available for research use in the near future during the project period of this award. A change in scope of the project was requested and granted by NASA. In addition, a change in P.I. to Bryan J. Tucker was granted by NASA and UCSD to more appropriately follow the new direction of research to better accommodate the change in scope of the project for NASA.

Statement of Work:

Objectives: This project was to examine the alterations in renal functions during skeletal muscle disuse in simulated microgravity. Although this area could cover a wide range of investigative efforts, the limited funding resulted in the selection of two projects. These projects would result in data contributing to an area of research deemed high priority by NASA and would address issues of the alterations in renal response to vasoactive stimuli during conditions of skeletal muscle disuse as well as investigate the contribution of skeletal muscle disuse, conditions normally found in long term human exposure to microgravity, to the balance of fluid and macromolecules within the vasculature versus the interstitium. These two projects selected are as follows: 1) Investigate the role of angiotensin II on renal function during periods of simulated microgravity and skeletal muscle disuse to determine if the renal response is altered to changes in circulating concentrations of angiotensin II compared to appropriate controls. and 2) Determine if the shift of fluid balance from vasculature to the interstitium, the two components of extracellular fluid volume, that occur during prolonged exposure to microgravity and skeletal muscle disuse is a result, in part, to alterations in the fluid and macromolecular balance in the peripheral capillary beds, of which the skeletal muscle contains the majority of recruitment capillaries. A recruitment capillary bed would be most sensitive to alterations in Starling forces and fluid and macromolecular permeability.

Progress Report: The two projects were completed with data from the first project presented at the 1993 FASEB meeting in New Orleans, Louisiana with a paper in preparation. The second project was completed and the initial results discussed with Dr. Peter Norsk and Dr. Lars Bo Johansen of the DAMEC Research Inc., Copenhagen, Denmark (an integral portion of the European Space Agency) which led to an informal collaboration. As a result of this collaboration, the findings from the second project which indicated increased macromolecular escape from the vasculature during conditions of prolonged simulated microgravity and skeletal muscle disuse (which were performed in rats), were also observed in humans submitted to head-out water immersion for 12 hr and may lead to a better understanding of the alterations in fluid volume homeostasis during prolonged spaceflight.

1. Effects of angiotensin II infusion on glomerular hemodynamics and tubular reabsorption in 14 day head-down tilt rats.

We have completed studies examining the effects of angiotensin II infusion in both 14

day head-down tilt (HDT) and in tail suspended non-tilt controls. Previous studies from our laboratory have demonstrated that at 14 days HDT plasma volume is significantly reduced and extracellular fluid volume is not different from pre-tilt values. In humans, plasma renin activity is not different from normal after extended HDT, bed-rest, or spaceflight. Long term negative fluid and electrolyte balance from prolonged exposure to microgravity conditions should result in responses, similar to chronic salt depletion, where there is either downregulation or no change in glomerular angiotensin II receptors. Therefore, infusion of exogenous angiotensin II should produce the same or reduced renal vasoconstriction in HDT rats compared to that of non-tilt controls. However, when angiotensin II was infused at the same dose in both HDT and non-tilt controls, producing a similar increase in systemic blood pressure, there was a greater vasoconstrictive effect in the HDT down-tilt rats compared to controls. This resulted in a significant decrease in both glomerular filtration rate and single nephron glomerular filtration rate in HDT rats compared to non-tilt controls (Figure 1). The reduction in nephron filtration rate in HDT rats was due to reductions in both nephron plasma flow (from 128 ± 10 to 67 ± 4 nl/min in HDT after AII, $P<0.05$) and the glomerular ultrafiltration coefficient (from 0.060 ± 0.011 to 0.027 ± 0.004 nl/sec·mm Hg in HDT after AII) that was insufficiently opposed by the increase in the glomerular hydrostatic pressure gradient. These unexpected renal responses to AII infusion in HDT are similar to a response observed in plasma volume expanded rats, and not in euvolemic or volume depleted conditions. These data indicate that glomerular angiotensin II receptors may be increased in 14 day HDT compared to non-tilt controls. This results in a disproportionate response to angiotensin II considering the volume status of the rat. Measurement of glomerular AII receptors in 14d HDT and non-tilt controls would be a likely followup area of investigation. One potential stimulus for upregulation of angiotensin II receptors in the glomerulus is a reduction in renal sympathetic activity. These data clearly demonstrate the need for further understanding of the dynamics of the neurohormonal axis in HDT and potentially spaceflight and that extrapolation of data from circulating hormone levels and volume status would, at best, only provide partial information. This dissociation between angiotensin II response and volume status has not been previously observed. If skeletal muscle disuse, cardiovascular alterations contributing to orthostatic intolerance, and negative fluid balance alter angiotensin II activity, the enhanced renal response to angiotensin II and the

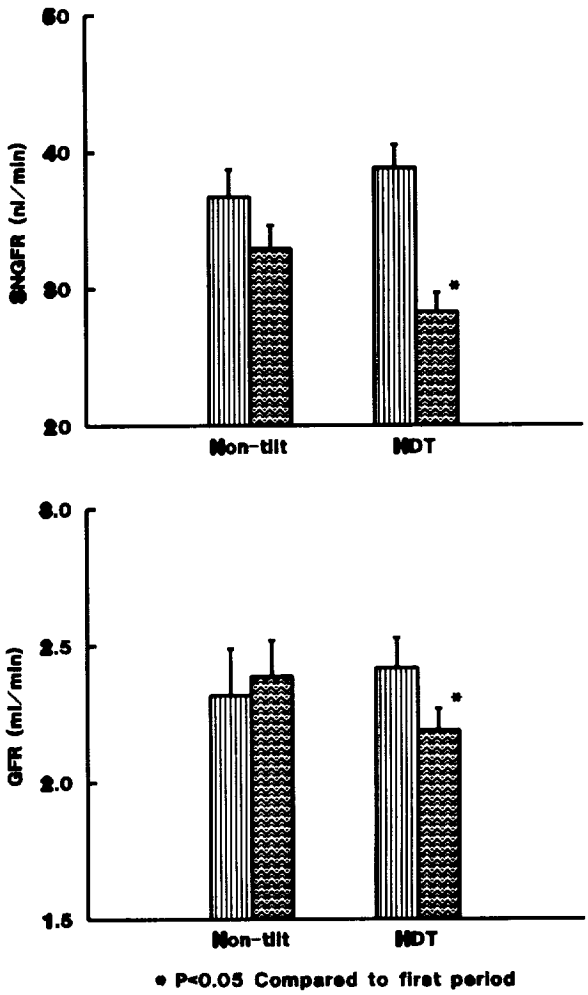

Figure 1. Effect of angiotensin II infusion on GFR and SNGFR in Non-tilt and after 14 day HDT. The paired bars are before and after AII infusion respectively.

resulting effect on renal function must be considered.

Another observation resulting from this study is that despite a greater reduction in single nephron filtration rate after angiotensin II infusion in HDT rats compared to non-tilt controls, both early distal tubule flow rate (7.6 ± 0.7 vs 7.5 ± 0.7 nl/min, NS) and the resulting urine flow (3.8 ± 0.5 in HDT vs 3.4 ± 0.7 μl/min) were not altered indicating a resetting of glomerular-tubular balance.

These findings are critical to the further understanding of the physiologic response to simulated microgravity and indicate resetting of the mechanisms responsible for renal function control, responses that would not have been predicted from volume status alteration studies. A portion of these studies have been presented and a manuscript is in preparation.

2. Evidence of increased systemic transcapillary albumin escape rate (TER_{alb}) after 30 days of head-down tilt.

We have recently hypothesized that the dissociation in volume ratio between the plasma and interstitium is due to the shift in Starling forces to produce positive fluid movement from the distal portions of the capillaries and venules outward to the extravascular space in the upper torso and cephalad regions of the body as well as the capillaries residing in the skeletal muscle. This increased filtration in these regions will produce edema and may not be totally compensated by the reverse fluid movement in the lower portion of the body. This hypothesis is testable by examining the systemic transcapillary escape rate of albumin (TER_{alb}) due to the differences in macromolecular permeability between normal filtering and reabsorbing sections of the peripheral vasculature. In some initial studies, we found that at 30 days HDT, TER_{alb} was significantly increased compared to non-tilt controls (Figure 2). In these rats, blood volume was less than non-tilt controls, whereas hematocrit and systemic plasma protein concentration was not significantly altered. Renal interstitial volumes were also obtained in 30 day HDT rats and were found not to be different from control (23 ± 1 vs 22 ± 1% of kidney volume, respectively). The increased systemic TER_{alb} may help define the mechanisms responsible for the significant and persistent decrease in plasma volume with little or no alteration of ECF during HDT. These findings were recently confirmed in humans with 12 hr head-out water immersion, utilizing Evans blue labeled albumin (personal communications). These data indicate that either pressure or macromolecular permeability alterations occur in the peripheral vascular beds, in which skeletal muscle plays a major role, and influence the balance of vascular and extravascular fluid and could contribute to the orthostatic intolerance associated with return to normal gravity environments after prolonged exposure to microgravity. A better understanding of this issue and future investigation may provide a effective countermeasure to the loss of plasma volume, which contributes to orthostatic intolerance upon return from exposure to microgravity conditions.

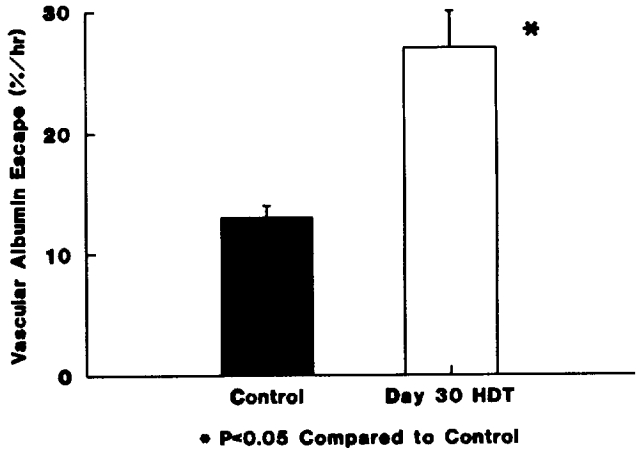

Figure 2. Systemic transcapillary albumin escape rate alterations after 30 days HDT.

Publication:

1. Tucker, B.J. and M.M. Mendonca. Increased renal hemodynamic response to angiotensin II during simulated microgravity in the rat. Presented at the annual meeting of FASEB (Experimental Biology 93), 1993. The FASEB J., 7:A667, 1993.

Formal seminars presenting work accomplished on NCC 2-556:

1. Invited Speaker, NASA-Ames Life Sciences Seminar Series, Mountain View, California (6/92).

2. Invited Speaker, Danish Aerospace Medical Center for Research, Copenhagen, Denmark (8/92).

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